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Outcomes of Patients With Colorectal Liver Metastasis in the Developing World: Is Liver Transplantation for Unresectable Liver Metastasis, the Next Logical Step?

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Background: **While half of the patients with colorectal cancer develop metastasis, some 20% develop liver-only disease, and 10% of patients with unresectable liver disease live for 5 years. This study audits the outcomes of patients with colorectal liver metastasis to identify patients with unresectable liver metastasis eligible for a liver transplant.** ***Method:*** **All patients with colorectal liver metastasis, irrespective of the presence of metastasis at other sites, registered between January 1, 2018, and December 31, 2019, were included in this retrospective audit. Patients in whom R0 Resection with adequate future liver remnant was not possible even after downstaging with chemotherapy were deemed unresectable. Overall survival was calculated using the Kaplan–Meier analysis. Patients eligible for a liver transplant were identified using the International Hepato-Pancreatico-Biliary Association (IHBPA) consensus guidelines and Oslo and Fong clinical risk scores.** ***Results:*** **Out of 284 patients, 80 were treated with curative intent and 185 with palliative intent. At a median follow-up of 36 months, the median and 3-year OS were 37 months and 55% for the curative intent group and 9 months and 4% for the palliative intent group, respectively. Among 173 patients with liver-only metastasis, 13 patients (7%) satisfied the IHBPA consensus guidelines and had both Oslo and Fong scores of 2 or less. Transplant-eligible patients with unresectable liver metastasis had median and 3-year OS of 24 months and 25% against 9 months and 5% for ineligible patients, respectively.** ***Conclusion:*** **Liver transplant has the potential to benefit a small but significant portion of patients with unresectable liver metastasis. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Colorectal cancer (CRC) is the most frequent digestive tract malignancy and the third most common cancer worldwide.[1] About half of the patients with CRC develop metastases at some point in the course of their disease, primarily to the liver and/or lung. Around 20% of the patients included in first-line chemotherapy studies develop liver-only disease.[2] Liver resection, considered the only curative treatment, is possible for only 20% of patients with colorectal liver metastasis (CRLM).[3] Even in patients who undergo resection, recurrence occurs in more than 50% due to undetected metastasis in the remnant liver.[1] Most studies have reported 5-year overall survival (OS) of 30%–40%[2] for resected CRLM. For patients with unresectable disease, palliative systemic chemotherapy is the only available treatment option and the 5-year OS is hardly 10%.[4]

Prospective studies on liver transplantation (LT) for unresectable liver metastasis have shown 5-year OS of 60–83%,[4] providing hope of improved survival with this modality albeit with the use of stringent selection criteria.[1] In recent times, there has also been a renewed interest in using hepatic artery infusion chemotherapy (HAIC) to increase resectability and control disease progression in the liver in patients with a liver predominant disease.[5]

In the Indian subcontinent, more patients present with an advanced stage and 28% of the patients were metastatic at presentation with the liver (14%) being the most common site.[6] However, the literature on the outcomes of CRLM in such resource-limited settings is scarce, and LT for unresectable CRLM is virtually unheard of. In this study, a retrospective audit on the outcomes of patients with CRLM has been done to assess if there were sufficient

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Abbreviations: CEA: carcinoembryonic antigen; CRC: colorectal cancer; CRLM: colorectal liver metastasis; EMR: electronic medical records; FCR score: fong clinical risk score; HAIC: hepatic artery infusion chemotherapy; IHBPA: International Hepato-Biliary–Pancreatic Association; LDT: liver-directed therapy; LT: liver transplantation; MDAC: moderately differentiated adenocarcinoma; MSI-H: microsatellite instability-high; MTV: metabolic tumour volume; OS: overall survival; SECA I: secondary cancer I
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patients to initiate a referral program for LT for unresectable CRLM.

METHODS

Study Design, Setting and Patients

The electronic medical records (EMR) of our institute, a tertiary referral centre in South Asia, were searched to identify patients with CRLM registered in the institute between January 1, 2018, and December 31, 2019. The inclusion criteria for this retrospective observational study were.

- CRLM patients aged 18 years or older treated during this period, irrespective of the presence or absence of extra-hepatic metastasis
- Primary adenocarcinoma histology
- Both synchronous and metachronous liver metastasis
- Both curative or palliative intent patients including those who were declared unfit for any cancer-directed therapy

Patients with CRLM and other primary histologies such as squamous cell carcinoma, neuroendocrine carcinoma and melanoma were excluded from the audit.

The International Hepato-Biliary–Pancreatic Association (IHBPA) consensus guidelines for LT for unresectable liver metastasis were used to identify patients with unresectable CRLM who were eligible for LT.[1] Patients with unresectable liver metastasis without extra-hepatic metastasis, microsatellite instability-high (MSI-H) status and BRAF v600E mutations were first identified. Patients were classified according to the timing of metastasis as synchronous and metachronous, and patients with synchronous metastasis were further subdivided according to the symptoms due to the primary disease as symptomatic and asymptomatic. Response to bridging therapy was then assessed in all the patients. Bridging therapy could be with 5-fluorouracil-based or oxaliplatin-based or irinotecan-based regimens. The response assessment was done three monthly, and Response Evaluation Criteria In Solid Tumours (RECIST, version 1.1) were used for the response assessment. Patients with metachronous liver metastasis received 6 months of bridging chemotherapy. Patients with synchronous liver metastasis and symptomatic primary received surgery for the primary followed by six months of bridging therapy, while patients with asymptomatic primary received six months of bridging therapy with surgery planned at three months if there was a response to chemotherapy. In this retrospective study, none of the asymptomatic patients underwent surgery. Patients who progressed or had a response <10% during the chemotherapy for 6 months were excluded. Patients who had progression beyond 6 months of chemotherapy but within tone year of diagnosis of metastasis were also excluded, and thus LT would be only offered to those patients without progression at 1-year post-diagnosis of metastasis.[4]

Oslo and Fong clinical risk (FCR) scores were then calculated, and patients who did not have both of these scores ≤2 were excluded.[1] Four factors namely the size of the largest tumour of more than 5.5 cm, carcinoembryonic antigen (CEA) of more than 80 μg per litre, duration between the primary surgery and LT of fewer than 2 years and progression of the metastasis before LT were given 1 point each for the calculation of the Oslo score and are used for prognostication post-LT.[2] The FCR score is used for prognostication in patients who undergo liver resection for CRLM and is calculated by giving 1 point each for the following factors: Metastasis detected less than 1 year from the diagnosis of primary, more than 1 liver metastasis, the size of the largest tumour of more than 5 cm, carcinoembryonic antigen (CEA) of more than 200 μg per litre and a node-positive primary tumour.[1]

Variables

Data retrieved from EMR include age, sex, site of primary, sites and timing of metastasis, carcinoembryonic antigen (CEA), primary histology, clinical T and N stage, the intent of treatment, neoadjuvant therapy details, the surgery done for the primary, liver-directed therapy (LDT), the pathologic T and N stage, adjuvant therapy details, the site and timing of recurrence and progression, treatment for recurrence, systemic palliative therapy details, follow-up duration and the status on follow-up.

Caecum, ascending colon and transverse colon including splenic flexure was designated as the right colon and descending and sigmoid colon including the rectosigmoid as the left colon. The presence of liver metastasis at the time of diagnosis or at the time of surgery was considered synchronous, whereas the development of liver metastasis at a later time was considered metachronous.[7] Early metachronous was the development of liver metastasis within 1 year of completion of curative treatment for the primary, whereas late metachronous was the development of liver metastasis after 1 year of completion of curative treatment.[8]

Patients were classified as per the intent of treatment into curative and palliative. The intent was considered curative only if they received definitive treatment at both the primary and metastatic sites. Based on resectability, liver metastasis was classified into resectable, potentially resectable and unresectable. Patients in whom R0 Resection with adequate future liver remnant (FLR) with preserved vascular inflow and outflow and biliary drainage was possible at the time of diagnosis were deemed resectable. Potentially resectable was a term used when the liver disease would be amenable to resection after preoperative therapy or volume augmentation procedures. The term unresectable was used when it was felt that resection would not be possible even with preoperative therapy and volume augmentation procedures.[9] All decisions on resectability

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were taken in a multi-disciplinary meeting with both the surgeon and a radiologist present. Overall survival (OS) was defined as the interval between the start of the treatment for the metastasis and the last follow-up or death as the study population was heterogeneous.

Statistical Methods

Categorical variables were expressed as numbers and proportions. For continuous variables, the median with the interquartile range was calculated. Comparison between categorical variables was done with Pearson chi-square test and that between continuous variables was done with the Mann Whitney log-rank test. The median follow-up was calculated using the reverse Kaplan–Meier method. Overall survival was calculated using Kaplan–Meier curves and was the primary end-point. Patients who defaulted without taking any treatment in our centre were not included in the survival analysis. The survival outcomes of different groups were compared using the Mantel–Cox log-rank test. Cox regression analysis was used to calculate the hazard ratio for death of the subgroups. A *P*-value of less than 0.05 was considered significant. Data recording and statistical analysis were done using IBM SPSS version 28.0 (IBM Corp., NY, USA). The Institutional ethics committee approval was waived off given the study's retrospective nature with all data, including follow-up, being retrieved from EMR and as none of the patients were contacted for follow-up either in person or telephonically.

RESULTS

Baseline Characteristics

Between January 1, 2018, and December 31, 2019, 284 patients with CRLM were treated at our centre. The median age was 50 (range, 19–89) years, and 188 patients (66.2%) were males. Left-sided primaries contributed to most CRLM and were seen in 231 patients (81.3%). Liver-only metastasis at baseline was seen in 173 patients (60.9%), and the remaining 111 patients (39.1%) had metastasis at other sites along with liver metastasis. Synchronous liver metastasis was seen in 219 patients (77.1%). Unresectable liver metastasis at baseline was seen in 138 patients (48.6%) in the whole cohort of 284 patients and 73 patients (42.2%) in the cohort of 173 patients with liver-only metastasis. Moderately differentiated adenocarcinoma (MDAC) was the predominant histology seen in 190 patients (66.9%). In the whole cohort of 284 patients, 80 (28.2%) were treated with curative intent, 185 (65.1%) with palliative intent and 19 (6.7%) were lost to follow-up. In the cohort of 173 patients with liver-only metastasis, 66 (38.15.%) were treated with curative intent, 93 (53.75%) with palliative intent and 14 (8.1%) were lost to follow-up. Table 1 shows the baseline characteristics of the whole cohort of 284 patients.

Treatment Characteristics

In the group treated with curative intent, 29 patients (36.3%) received chemotherapy before resection, and 25 out of the 27 (92.59%) rectal cancer patients received pre-operative radiotherapy. Surgery as the LDT or part of LDT was performed in 50 patients (62.6%). In the group treated with palliative intent, 156 patients (84.3%) received first-line palliative chemotherapy, whereas only 85 patients (46%) could receive

Table 1 Baseline Characteristics of the Whole Cohort of Patients With Colorectal Liver Metastasis.

Patient characteristics		Number of patients (n = 284)
Male/Female		188 (66.2%)/ 96 (33.8%)
Median age (years)		50 (range 19–89)
Site of the primary	Right Colon	53 (18.7%)
	Left Colon	75 (26.4%)
	Rectosigmoid	38 (13.4%)
	Rectum	118 (41.5%)
Sites of metastasis	Liver only	173 (60.9%)
	Liver with lung	28 (9.9%)
	Liver with other sites	83 (29.2%)
Timing of metastasis	Synchronous	219 (77.1%)
	Early Metachronous	23 (8.1%)
	Late Metachronous	42 (14.8%)
Median CEA (ng/ml) at baseline with range		31.63 (1.46–57,548)
Histology	WDAC	13 (4.6%)
	MDAC	190 (66.9%)
	PDAC	36 (12.7%)
	Signet ring cell adenocarcinoma	6 (2.1%)
	Mucinous adenocarcinoma	2 (0.7%)
	Adenocarcinoma	37 (13%)
Liver resectability at baseline	Resectable	99 (34.9%)
	Potentially Resectable	47 (16.5%)
	Unresectable	138 (48.6%)
cT	T1	1 (0.4%)
	T2	8 (2.8%)
	T3	213 (75%)
	T4	62 (21.8%)
cN	N0	14 (4.9%)
	N1	117 (41.2%)
	N2	153 (53.9%)
Intent of treatment	Curative	80 (28.2%)
	Palliative	185 (65.1%)
	Lost to follow up	19 (6.7%)

Abbreviations: CEA – Carcinoembryonic antigen; WDAC – Well-differentiated adenocarcinoma; MDAC – Moderately-differentiated adenocarcinoma; PDAC – Poorly-differentiated adenocarcinoma; cT – clinical tumour stage; cN – clinical nodal stage.

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second-line chemotherapy. Supplementary Tables 1 and 2 show the treatment characteristics of the cohorts treated with curative and palliative intents, respectively.

Survival Outcomes

At a median follow-up of 36 (range, 1–49) months, the median OS was 37 months for the curative intent group and 9 months for the palliative intent group and the 3-year OS was 55% and 4%, respectively. In the group of patients who had liver-only metastasis, at a median follow-up of 37 (range 1–49) months, the median OS was 39 months for the curative intent group and 10 months for the palliative intent group and the 3-year OS was 55% and 6%, respectively. Figure 1A depicts the survival curves of the patients treated with curative and palliative intents in the whole cohort and the liver-only metastasis cohort.

Synchronous vs Metachronous Metastasis

Patients with synchronous metastasis had more left colonic primaries [65 (29.7%) vs 10 (15.4%)] and fewer rectal primaries [82 (37.4%) vs 36 (55.4%); $P = 0.042$]. The median CEA at the diagnosis of liver metastasis was significantly higher in the synchronous group (42.46 vs 11.58, $P = 0.002$). The Synchronous group also had more poorly differentiated tumours [31 (14.2%) vs 5 (7.7%); $P = 0.003$], heavier nodal burden [N2 133 (60.7%) vs 20 (30.8%); $P < 0.001$], more unresectable liver metastases [122

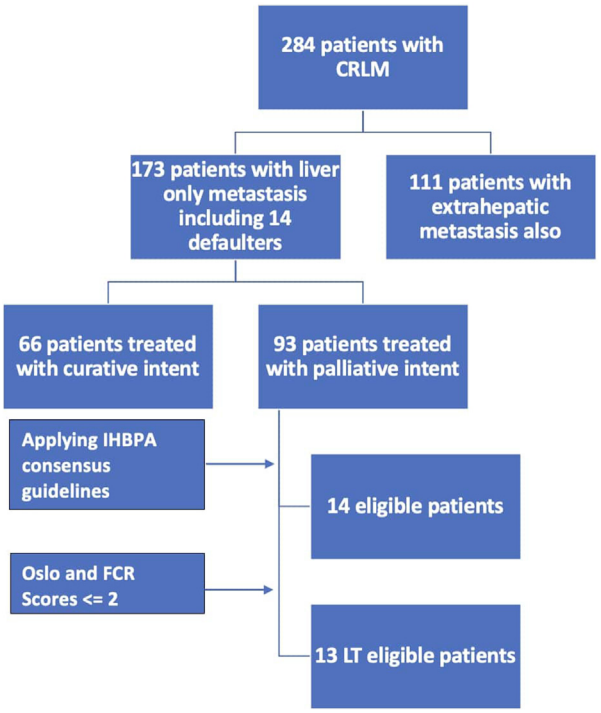

Figure 2 Flowchart depicting the selection of liver transplant-eligible patients from the whole cohort of patients with colorectal liver metastasis. Abbreviations: CRLM – colorectal liver metastasis, IHBPA – International Hepato-Biliary-Pancreatic Association, FCR Score – Fong's Clinical Risk Score, LT – Liver Transplant.

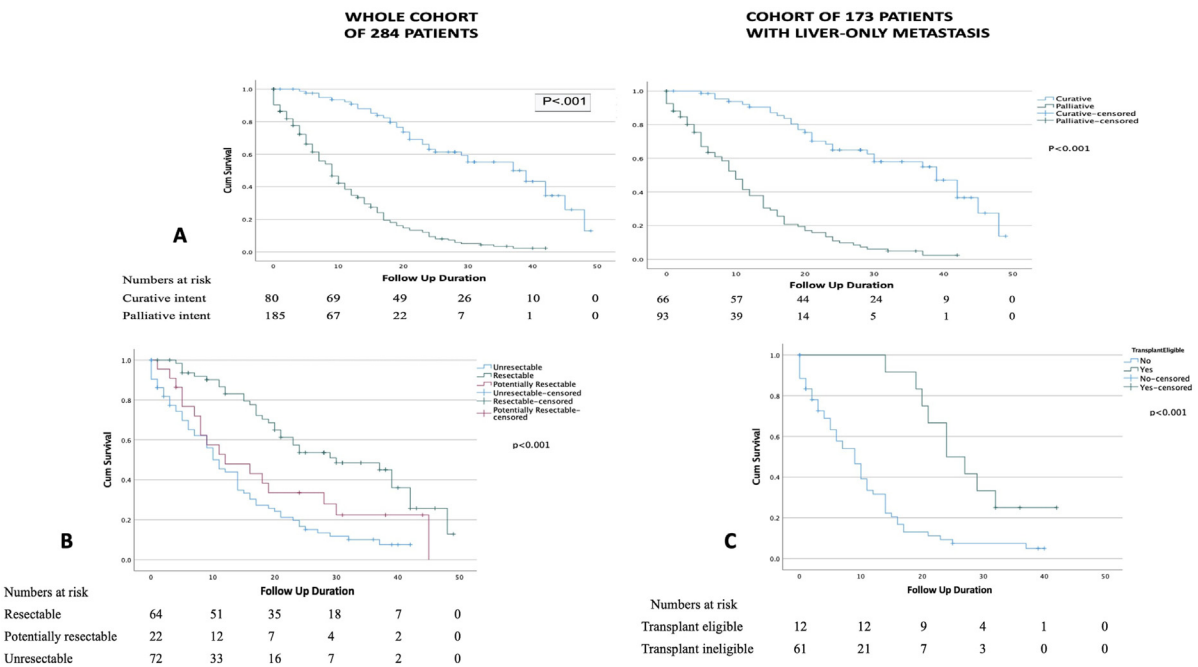

Figure 1 (A) Comparison of overall survival of patients treated with curative and palliative intents in the whole cohort of patients with colorectal liver metastasis on the left and in the cohort of patients with liver-only metastasis on the right. (B) Comparison of overall survival of patients with resectable, potentially resectable and unresectable liver metastasis at baseline in the cohort of patients with only colorectal liver metastasis. (C) Comparison of overall survival of transplant-eligible and -ineligible patients in the cohort of patients with unresectable colorectal liver metastasis only.

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(55.7%) vs 16 (24.6%); $P < 0.001$] and fewer patients treated with curative intent [45 (20.5%) vs 35 (53.8%); $P < 0.001$]. The synchronous group had a median OS of 13 months compared to 18 months for the metachronous group ($P < 0.001$). Supplementary Table 2 shows a comparison between synchronous and metachronous groups.

Transplant Eligibility

Among the 173 patients with liver-only colorectal metastasis, 13 patients (7%) satisfied the IHBPA consensus guidelines and had both Oslo and FCR scores of ≤2. Figure 2 shows the flowchart depicting the selection of transplant-eligible patients. The Oslo score was 1 for 11 patients (84.6%) and 2 for the remaining 2 patients (15.4%). Among these 13 patients, 12 patients were unresectable at baseline and on the completion of 6 months of chemotherapy and 1 patient had an unresectable recurrence which remained unresectable post 6 months of chemotherapy. While the median OS of the whole group of 73 patients who had unresectable liver metastasis was 11 months, the subgroup which was transplant-eligible had a median OS of 24 months against 9 months for the subgroup which was ineligible ($P < 0.001$). The 3-year OS was also significantly better for the transplant-eligible subgroup (25% v/s 5%). Figures 1B and 1C depict the survival curves of the liver-only metastasis cohort as per resectability and the unresectable liver-only metastasis cohort as per transplant eligibility. The hazard ratio for death for transplant-ineligible patients compared with transplant-eligible patients was 3.442 (CI 1.658–7.147). With only systemic chemotherapy, out of the 13 transplant-eligible patients, 10 patients (76.9%) had progression in only the liver, 2 patients (15.4%) had progression in both the liver and lungs and 1 patient (7.7%) had progression in the liver, lungs and periportal lymph nodes. Table 2 shows the characteristics of the transplant-eligible subgroup of 13 patients.

Table 2 Characteristics of Liver Transplant Eligible Sub-group of Patients With Unresectable Colorectal Liver Metastasis.

Patient characteristics		Number of patients (n = 13)
Male/Female		8 (61.5%)/ 5 (38.5%)
Median age with range (years)		54 (29–62)
Site of primary	Right Side	1 (7.7%)
	Left Side	12 (92.3%)
Timing of metastasis	Synchronous	12 (92.3%)
	Metachronous	1 (7.7%)
Histology - MDAC		13 (100%)
Molecular criteria	Ras mutated	3 (23.1%)
	Raf mutated	0
	MSI-H	0
cT	T3	12 (92.3%)
	T4	1 (7.7%)
cN	N0	1 (7.7%)
	N1	12 (92.3%)
Median size of largest lesion with range (cm)		3.60 (1.50–4.90)
Surgery for the primary		4 (30.8%)
T4 and/or N2 status post neoajuvant therapy		0
CEA at diagnosis of metastasis >80 ng/ml		6 (46.2%)
Increasing trend of CEA with chemotherapy		0
Chemotherapy used	Oxaliplatin based	12 (92.3%)
	Irinotecan based	1 (7.7%)
	Biological agent used	6 (46.2%)
Partial response to 6 months of chemotherapy		13 (100%)
Liver resectable post 6 months of chemotherapy		0
Progression at 1 year post diagnosis of metastasis		0
CEA at 1 year post diagnosis of metastasis >80 ng/ml		1 (7.7%)
Oslo score	1	11 (84.6%)
	2	2 (15.4%)
Organ of progression beyond 1 year of diagnosis of metastasis	Liver only	10 (76.9%)
	Liver and lung	2 (15.4%)
	Liver, lung and periportal lymph nodes	1 (7.7%)

Abbreviations: MDAC – Moderately-differentiated adenocarcinoma; MSI-H – Microsatellite Instability – High; cT – clinical tumour stage; cN – clinical nodal stage; CEA – Carcinoembryonic antigen.

DISCUSSION

Hardly one-third (28.2%) of the patients with liver metastasis in this series underwent curative intent treatment. The median OS for the patients treated with curative intent was 37 months and 3-year OS was 55%. In the western world, it has been estimated that 20–30% of patients with liver metastasis would be candidates for curative resections,[10] and the 5-year OS for the population which underwent curative resection has been estimated to be between 37 and 58% in recent series.[11] Although the patients in this series underwent both resections and ablation, the outcomes in this series are in the range of those reported in the literature. However, the median OS for the patient treated with palliative intent was only 9 months, more dismal than that reported in the literature.[4] The dismal prognosis of unresectable CRLM with systemic chemotherapy alone as well as improvements in the outcomes of liver transplant along with the development of novel immune suppressants has rekindled interest in LT as a therapeutic option.[2] LT also offers the advantage of removing undetected metastasis from the apparently normal liver.[1]

The first study on liver transplant for unresectable CRLM in recent times, the Secondary Cancer I (SECA-I) trial obtained an estimated 5-year OS of 60% despite having a heterogenous cohort[4] and most patients having a

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recurrence within a median of six months.[1] The multicentric retrospective study of the Compagnons Hépato-Biliaires also showed a 5-year OS of 50%.[1] The SECA-II trial used more stringent selection criteria and obtained a 5-year estimated OS of 83%.[4] When the SECA I patient group was compared to a group of similarly matched patients from the Nordic VII trial who received chemotherapy only, the 5-year OS was 56% in the SECA I group versus 9% in the Nordic VII group.[2] The long-term follow-up of the SECA I study showed an actuarial 5-year OS of 43.1%.[12] These results lend support to LT as a treatment option for unresectable liver metastasis albeit in highly selected patients.[1]

The SECA I trial also led to the development of the Oslo score used for prognostication post-transplant for CRLM.[1] The IHPBA guidelines provide an excellent framework for patient selection for LT, and along with the Oslo score, the FCR score and metabolic tumour volume (MTV), which should be less than or equal to 70 cm^3, provide stringent patient selection criteria for LT.[1] In this series, over two years, 13 patients from among 173 patients with liver-only colorectal metastasis met the eligibility criteria for LT. This meant that 7% of the patients with liver-only colorectal metastasis and around 16% of patients with unresectable liver-only colorectal metastasis at baseline would be eligible for LT.

The survival of transplant-eligible patients with unresectable metastasis was significantly better than that of non-eligible patients (3-year OS 25% v/s 5%) even without LT, suggesting that these patients may have better tumour biology. However, the survival of the LT-eligible patients in this series is hardly half of that reported in prospective studies of LT. LT may, therefore, more than double the survival of this group of highly selected patients. HAIC, which is an aggressive liver-directed therapy for patients with unresectable liver predominant disease, may close in on this survival gap between LT and palliative chemotherapy. When used along with systemic therapy, responses were seen in up to 92% and 85% of chemotherapy naöve patients and pre-treated patients, respectively. Prospective studies have shown conversion to resectability rates up to 52%.[13] The recently published University of Miami experience with HAIC showed that 41% of initially unresectable patients underwent complete removal of their liver disease by either resection or ablation following HAIC and systemic chemotherapy, and the median OS for the resected group post-HAI was 20 months.[14] These results suggest that HAIC with systemic chemotherapy could be used as a better bridge to LT than systemic chemotherapy alone.

The long-term follow-up of the SECA I showed that the 5-year OS was 75% for patients with an Oslo score of 1 and 50% for patients with an Oslo score of 2.[12] Most of the patients in this series (84.6%) had an Oslo score of 1 and only 2 patients (15.4%) had an Oslo score of 2, and hence the entire group can be expected to have good overall survival. At the time of progression, all patients had progression in the liver and most patients (76.9%) had progression in only the liver. Moreover, in this series, the survival of the patients with only CRLM is not significantly different from that of patients with metastasis at other sites in addition to CRLM, suggesting that survival would depend on the tumour burden in the liver. These observations suggest that removing the tumour-laden liver might significantly increase the survival, justifying this highly complex procedure for this select group of patients, who otherwise do not have any other viable treatment option.

The most significant issues with this novel indication for LT in resource-limited settings would be the availability of graft for LT and the cost of the procedure. If waitlisted for a cadaveric graft with a MELD (model for end-stage liver disease) score, these patients are unlikely to receive extra points which are given to primary HCC and would be given the least preference in addition to being subjected to ethical issues associated with using a graft for a relatively unknown indication. The use of living donor grafts, extended donor criteria donors and Rapid technique using both living and deceased donor grafts can circumvent these problems[4] and provide a way for instating transplant programs for unresectable liver metastasis. In today's era, with expanding indications for a liver transplant for both hepatocellular carcinoma and intrahepatic cholangiocarcinoma,[15] LT for unresectable CRLM is perhaps the next logical step forward.

Our institute currently offers systemic chemotherapy for patients with unresectable CRLM at presentation. If the disease is liver-limited, post chemotherapy, LDT is offered as per the burden of the disease. HAIC is offered for liver-limited progression, and LT is considered for selected patients with unresectable liver metastasis eligible for the same.

This study has a few limitations. The retrospective nature of this study with its associated selection bias is the first limitation. Secondly, most of the patients in this series did not have a PET CECT scan, so the MTV could not be calculated. However, it is known that the MTV correlates with both Oslo and Fong's scores, and since only patients with both scores ≤ 2 were considered eligible in this series, all the eligible patients could also be expected to have MTV ≤ 70 cm^3. The complex nature of LT warrants the calculation of MTV for all eligible patients, and a PET scan both at baseline and for response assessment should be done. Thirdly, none of the LT-eligible patients with synchronous liver metastasis had surgery done for their primary as they were all asymptomatic and were not planned for LT, and the effect of the untreated primary on the outcomes is unknown. However, the CT scan done 1 year post-diagnosis, the estimated time of the liver transplant showed resectable disease with response to chemotherapy and no evidence of progression.

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The prognosis of unresectable colorectal liver metastasis treated with systemic chemotherapy alone is still dismal. A liver transplant with stringent patient selection has the potential to benefit a small but significant portion of patients with unresectable liver metastasis, and timely referral of eligible patients to a liver transplant centre is warranted.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

M Janesh, first author – Conceptualisation, Investigation, Data Curation, Formal analysis, Writing - Original Draft, Writing - Review & Editing and Visualisation.

Mufaddal Kazi - Conceptualisation, Formal analysis, Writing - Original Draft, Writing - Review & Editing and Visualisation.

Shraddha Patkar – Corresponding author - Conceptualisation, Formal analysis, Writing - Review & Editing, Visualisation and Supervision.

S Prudvi Raj - Investigation, Data Curation and Writing - Review & Editing.

Abhiram Bhoyar – Data Curation.

Ashwin Desouza – Formal analysis, Writing - Review & Editing and Visualisation.

Avanish Saklani – Conceptualisation, Writing - Review & Editing, Visualisation and Supervision.

Mahesh Goel – Conceptualisation, Writing - Review & Editing, Visualisation and Supervision.

CONFLICTS OF INTEREST

The authors have none to declare.

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DISCLOSURES

None.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2023.03.009.

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